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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING CARRIERS FOR PRODUCTS BASED ON VITAMIN-E, PA-
PAIN AND HYALURONIDASE

(57) Abstract: The present invention application refers to a new pharmaceutical composition comprising carriers for products to be
aggregated to the base of vitamin-E, papain and hyaluronidase in the following quantities: Papain 0.2 to 15 %, Hyaluronidase 50 to
900 utr/mg, Vitamin-E Oleosa 10 to 2000 mg.

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**"PHARMACEUTICAL COMPOSITION COMPRISING CARRIERS
FOR PRODUCTS BASED ON VITAMIN-E, PAPAIN AND
HYALURONIDASE"**

The present invention refers to a new
5 pharmaceutical composition, to be used in any
pharmaceutical form, most notably gel, cream,
aerosol and spray, liquid and liophilized, of a
carrier substance for products to aggregate vitamin-
E, papain and HYALURONIDASE. The above mentioned
10 pharmaceutical composition is of topical
application, non-toxic and features a high
penetration rate through the skin.

BRIEF DESCRIPTION OF THE INVENTION

The skin permeability varies according to the
15 region of the body, being the skin folds and the
face those that present the highest absorption rate.
A product applied over the skin will present a
longer period of contact and percutaneous absorption.

According to the classic book "Histologia dos
20 epiteliuns", by Walter A. Hadler and Sineli R.
Silveira, Editora Campus, Campinas, 1993, it is
considered that: "bearing in mind the general
morphological characteristics and the specialized

functions that they perform, the epithelium cells are predominantly classified into two categories, which correspond to two epithelium classes: coating epithelium cells and secreting epithelium cells. The
5 cells of these two classes mix with each other to constitute, respectively, the coating epitheliums and the secreting epitheliums, each one of them performing specific functions that are inherent to them. Such division is also fundamented in the
10 distribution of these two classes of epithelium in the organism, which although wide is is distinctive for both. With the purpose of forming the coating epitheliums the epithelium cells associate side-by-side, so as to originate "membranes" or layers
15 superimposed over the base membrane, which function is to coat surfaces. On the contrary, the secreting cells unite to form organized functional units, better suited for performing their specialized function, related to the secretion products
20 synthesys; thus are constituted the secreting units. The coating epitheliums are defined as living membranes, usually featuring a discontinuity, that isolate the organism from the environment,

separating the internal media from the external one. Furthermore, these epitheliums isolate from each other the various internal media compartments, among which are the intravascular compartment, the serum
5 compartment and several others. Among the various functions performed by the coating epitheliums some are performed by specialized variants that are specifically adapted to perform one or more functions. Others are incorporated as general
10 functions presented without distinction by every coating epithelium cell. The coating epithelium cell, in the same way as most of the living cells, passively absorbs water and electrolytes and eliminates them actively; this function is well
15 developed in the epithelium cells. On that account it is very important to observe that generally it is understood as absorption the penetration of solutions through the cells plasmatic membrane. However two different specific forms of absorption
20 must be distinguished from one another: the passive absorption, that occurs according to the osmotic laws, and the active absorption, that entails the effective participation of the epithelium cell and

that does not follow such physic laws. On the other hand it must be considered that every single substance that penetrates the interior of a multicellular organism, or else is excreted or
5 eliminated, must cross at least one coating epithelium, because every superior organism is penetrated internally and externally by epitheliums. It must also be observed that the coating epitheliums, although continuously covering and
10 protecting those surfaces it coats, are not impervious at all; hat is why they do not behave as inert "membranes". On the contrary, they allow for the exchange of gases, water, several kinds of electrolytes and certain other solutes between the
15 internal and the external media, or between the various internal compartments, which characterizes its permeability. The coating epithelium cells limit in a controlled and selective way the permeability of the respective epitheliums, with the purpose of
20 protecting the organism and still participate of the control of its homeostasis. In order to perform such function the epitheliums are organized and arrange their cells in a special form, in order to build up

coatings which cells abbut the base membrane and are united with each other by means of intracellular junstions; in turn the cells are coated by the plasmatic membrane, which features special characteristics, and by the glycocup, both able to express well defined functional properties. The functional characteristics expressed by the plasmatic membrane portion that coats the cells apical surface are different from those expressed by the portion situated in its basal or basolateral face; such differences, which occur mainly on the funsjctional aspect, contribute for the remarkable degree of polarization expressed by the coating epithelium cells. The prime function performed by the coating epitheliums correspond essentially to the protection rendered to the surface that they coat, characterizing their protective coating function. Such function features a special characteristic, being a coating that, besides offering mechanical, physical and chemical protection to the coated surface, is not inert. The coating epitheliums are pervious, which allows for the controlled and selective passage of several products through its

wall. There are many evidences in favor of the idea that the coating epitheliums permeability constitutes a fundamental property, with significant functional expression, for it is essential for the performance of several functions featured by the epitheliums, even more so because it is selective and its permeability degree presents a wide variation. It is fairly well demonstrated that the permeability degree influences strongly the function performed by the coating epitheliums:

- 1) wide permeability;
- 2) reduced permeability and
- 3) absence of permeability.

When there is a wide permeability, the epitheliums allow intense metabolic exchanges through their walls, with poor control and selectivity of its permeability. In these circumstances the epithelium acts on the filtration and transfer of metabolites, these functions requiring little qualitative control; the exercise of these functions is subordinated to the epithelium intrinsic structure, which is adapted to act, mainly passively, being low the level of selective

permeability. The coating epitheliums whith a reduced degree of permeability, due to the characteristic that is so peculiar to them, present the property of partially controlling their own permeability, and
5 above all their selectivity. As a consequence, these coating epitheliums present selective permeability, which allows them to interfere and qualitatively control their functional activity, as well as making them more able to actuate over the homeostasis
10 control. The absence of epithelium permeability is correlated to the complex isolation of the coated surface and, on the other hand, to the better controlling of this epithelium function, because its cells, altough very poorly pervious, present
15 selective permeability. In this case the coated surface has its boundaries limited by a "membrane" impervious or very poorly pervious and very effective, that performs an important protective function, for it is able to discriminate exactly
20 what can cross the epithelium. The coating epitheliums permeability is such an expressive functional property that it has been used as an important

classification criterium to rank them in three classes:

- 1) pervious epitheliums;
- 2) poorly pervious epitheliums and
- 5 3) impervious epitheliums.

Because of their selective permeability, even in the inferior animals the epitheliums have assumed the function of coating the organism, constituting its external coating, with limiting and protective
10 properties, not only morphological but also functional. Their cells, in principle very similar, behaved as a semi-pervious "membrane" poorly effective that acted passively, but which function allowed the separation, tough precarious and more
15 morphological than functional, between the internal and the external media. It seem to be that the majority of the coating epitheliums acts as a barrier that prevents the free passive diffusion, because their permeability, which is selective, is
20 conditioned to several factors among which stands out the electric potential present in their cell's plasmatic membrane. The continuity of the epithelium coating is established as much through the intimate

abutment of adjacent cells as through the presence of intercellular union devices. The epithelium cells are enveloped by the glycocalyx, that also takes part of the coating function performed by the epithelium, in addition to aid the union between adjacent cells, because the intracellular adhesive is formed also by glycocalyx. Several experimental investigations confirm that the coating epitheliums selective permeability is associated to other specific functions expressed by their cells, namely: absorption, excretion and secretion. These functions, beyond their permeability, which constitutes their prime function, are responsible by the general functioning of the epithelium cell. The general functions performed by the coating epitheliums are basically the following:

- 1) surfaces protective coating function;
- 2) isolation and functional individualization of the internal media and of its distinct compartments, due to their cells selective permeability;
- 3) controlling the homeostasis of the internal medium and its compartments due to their cells ability to interfere in the epithelium selective

permeability; the epithelium cells manifest the capacity to effect the absorption, secretion and excretion; such functions interfere on the epithelium permeability;

- 5 4) performance of the metabolic functions due to their ability to effect hydrosalinic exchanges and to effect metabolytes transfers due to their cells and intracellular spaces high degree of poorly selective permeability;
- 10 5) transport of products along the epithelial surface due to the participation of the cilium;
- 6) sensorial perception and
- 7) germinative function.

Among these functions, the first four derive
15 mostly from the epithelium cells selective permeability, over which are additionally superimposed the additional affects corresponding to their properties of absorption, excretion and secretion. Among the general functions performed by
20 the coating epitheliums, the selective permeability is responsible by the efficiency regarding the ability to coat, protect and isolate the surfaces, as well as to effect the control of the homeostasis;

the passive absorption and the metabolytes transfer capacity are executed normally by the majority of the cells of these epitheliums, which demand only minor adaptations to become able to effectively
5 perform such functions. On the contrary, the functions of absorption, excretion and secretion depend of properties that develop successively and would become paramount, mostly in some specialized types of coating epithelium, which adapted following
10 a new and specific direction. The sensorial perception and the germinative function are more specific functions that are only manifest by certain epitheliums even more specialized. Considering their cell's morphological characteristics, the coating
15 epitheliums have been classified according to the same number of cellular extracts they bear in: simple (a single extract) and stratified (two or more extracts). Both the simple epitheliums and the stratified ones, conforming to their cell's format,
20 are in turn subdivided into pavementous, cubic or prismatic. The simple epitheliums are usually adapted to manifest wholly their most expressive fundamental property, that consists in their permeability, which

degree and selectivity vary. The simple coating epitheliums, constituted by a single layer of pavementous or cubic-prismatic cells, present major differences regarding their functional properties, correlated not only to their cell's morphology, but also to the intracellular space's properties. The simple pavementous epitheliums are usually very pervious; the cubic-prismatic ones are less pervious. The coating epitheliums permeability, in addition to being selective, is controlled by their cell's functional activity, although the control loses efficiency in the same order as the intracellular space's permeability increases. The cubic-prismatic epitheliums, being less pervious than the pavementous, are more effective to control their permeability. Based on the format of the epithelium cell, in its permeability and the coating epitheliums most common adaptations, it is possible to generate a provisional classification for these epitheliums. Thus, the simple coating epitheliums are divided into two classes: pavementous and cubic-prismatic. Each class is subdivided according to it's functional properties in open or pervious epitheliums, in semi-

occlusive or poorly-pervious and occlusive or
impervious. In the simple coating epitheliums
classification, the cubic epitheliums and the
prismatic epitheliums are usually considered
5 distinct, being defined and identified according to
the format of the epithelium cells that make them up.
However some functional studies have showed that the
correlation between form and function presents
several exceptions. For this reason a functional
10 classification is adopted considering predominantly
it's permeability. According to this criterium these
epitheliums are denominated cubic-prismatic
comprising the semi-occlusive and occlusive
epitheliums. Following the same criterium the
15 stratified stratified epitheliums can be subdivided
into: pavementous and cubic-prismatic. The
stratified epitheliums are adapted to perform
primarily the mechanical protection function,
because they are impervious or poorly pervious. The
20 epitheliums comprise, in addition to the cells, the
intercelular space and the base membrane, which
interfere in their permeability degree; their
permeability derives not only from their cell's

peculiar properties, responsible for the transcelular permeability way, but also from the presence of another permeability way of their walls, constituting the intercelular or paracelular way.

5. The transcelular way comprises two different ways that consist of the transmembranosa way and the transcanicular or trancitose way. It has been demonstrated, experimentally, that the coating epitheliums can be transposed by water and by substances of various natures, both through their epithelium cells (transcelular way) and through the way situated between their cells (intercelular way).

In the first instance the epithelium cell can effect the permeability control of the epithelium through its biological activity, making this process selective. As for the intercelullar way permeability, the epithelium cell, although not behaving in a totally passive form, does not interfere directly in the transport selectivity. The sole form of cell active participation, in this instance, comprises the determination, exceptionally, the enlargement of the corresponding intercelular space. By means of the action of the

microfilaments that constitute its cito-skeleton, the epithelium cell, specially those of certain types of simple coating epitheliums pavementous of the open type, can change its format and retract segments of its cytoplasma; thus being able to influence the size of the intercellular space and regulate it. It has been established that the transcellular permeability of the simple coating epitheliums is perfectly distinct from the intercellular permeability, because both are subordinated to very different mechanisms. The epithelium cell permeability, which is selective, is influenced by its biological activity; on the contrary, the intercellular permeability is totally passive, and thus is not selective. Several experimental results have confirmed that the transposition of solutions through the epitheliums is subject to multiple control mechanisms, among which is paramount the intrinsic functional activity of its cells. On the contrary, the intercellular space permeability is generally not controlled, because in this case the transposition of a molecule through the epithelium follows only the corresponding physical laws and is

directly related to its diameter, its electrical cargo and, obviously, to the intercelular space size; these three variables constitute the main limiting factors that interfere on the intercelular permeability of the simple coating epitheliums. The transcelular permeability of the simple coating epitheliums can be exercised through two distinct and independent ways: the transmembrane way, which is the true transcellular way, and the transcanicular way, which happens through the vesicles and the cannules or tubes of the vesículo-canalicular system, found inside the citoplasma of many types of coating epithelium cells". Consequently, the coating epitheliums are pervious, which allows the controlled and selective passage of various products through its wall. It is demonstrated that the permeability degree affects strongly the coating epitheliums function.

Three types of coating epitheliums are thus considered:

- 1- Of wide permeability;
- 2- Of reduced permeability;
- 3- Of nule permeability.

The purpose is to prove through the formulation that there is an intense metabolic exchange demonstrating that the epithelium actuates on the transfer of metabolytes. This penetration of substances is complete and gradual and trespasses these epithelium layers until it penetrates the small blood vessels, reaching the circulatory current.

There is a description of the molecules to estimate the coating epitheliums permeability. Ex.: Hemoglobine, Ferritine, Lipo-proteines and enzymes.

Is is also known the transcitose on the transposition of the epitheliums by the macro and micro molecules until the vascular eye depending of their association.

The object of the present invention is a **"PHARMACEUTICAL COMPOSITION COMPRISING CARRIERS FOR PRODUCTS BASED ON VITAMIN-E, PAPAIN AND HYALURONIDASE"**

The formulation of such pharmaceutical composition comprises particularly:

PAPAIN -0.2 to 15%

HYALURONIDASE.....50 to 900 utr/mg

VITAMIN-E.....10 to 2000 mg

More advantageously the formulation of the pharmaceutical composition comprises:

PAPAIN -0.5 to 5%
HYALURONIDASE.....50 to 900 utr/mg
5 VITAMIN-E.....10 to 2000 mg

This technique was proofed through studies performed with 08 outpatients, in 02 distinct sessions of double blind analysis. The delimited area measured 15x10 cm with the application of gel,
10 after 15 minutes the measurements were started through liquid chromatography coupled to mass spectrometry.

The comparisson of a confirm cream with the same active substance, for the purpose of calibration,
15 yielded the following results regarding the cream according to the present invention, with an analytical type of equal absorption area:

Confirm cream = area 131 vol. 0,54 = 8 hours;

Tested cream (invention) = area 131 vol. 0,54 =
20 2 hours.

The penetration relation equals to 100% of the required cream.

SOME SUBSTANCES TO BE CARRIED (MERELY FOREXAMPLE) :

- CUTANEOUS CICATRIZATORS
- PURE ANTIBIOTICS AND SULFA DERIVATIVES
- 5 - TOPICAL DERMATOLOGIC ANTI-FUNGUS AGENT
- TOPICAL RUBIFACIENT ANTIREUMATICS
- CORTICOSTEROIDS, ANTIMICOTICS, PURE AND ASSOCIATED ANTIBACTERICIDES
- TOPICAL ANTI-VARIX
- 10 - ANTI-HISTAMINIC ANTI-ITCH
- TOPICAL ANTIVIRALS
- TOPICAL LOCAL ANESTHETICS
- HORMONAL AND NON-HORMONAL ANTI-INFLAMMATORY
- HISTAMINE CLOROHYDRATE
- 15 - FILDENAFIL CITRATE
- FENTOLAMINA MESILATE
- ALPROSTADIL (Prostaglandine)

CLAIMS

1) "PHARMACEUTICAL COMPOSITION COMPRISING
CARRIERS FOR PRODUCTS BASED ON VITAMIN-E, PAPAIN AND
HYALURONIDASE" wherein such composition's
5 formulation presents as product carriers:

PAPAIN -.....0.2 to 15%

HYALURONIDASE.....50 to 900 utr/mg

VITAMIN-E10 to 2000 mg

2) "PHARMACEUTICAL COMPOSITION COMPRISING
10 CARRIERS FOR PRODUCTS BASED ON VITAMIN-E, PAPAIN AND
HYALURONIDASE", according to claim 1, wherein the
composition's formulation presents advantageously as
product carriers:

PAPAIN -.....0.5 to 5%

15 HYALURONIDASE.....50 to 900 utr/mg

VITAMIN-E10 to 2000 mg